The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. A complete list of Warning Letters issued is available on FDA's web site at: http://www.fda.gov/foi/warning.htm.

Bioresearch Monitoring

Warning Letters Issued to Eight Clinical Investigators Conducting Studies with Investigational Products

The FDA's Center for Biologics Evaluation and Research (CBER) issued Warning Letters to the following clinical investigators conducting research in human subjects using various investigational test kits:

- On November 5, 2004, CBER issued a Warning Letter to Timothy Purington, Tapestry Health Systems, Florence, Massachusetts. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to obtain informed consent in accordance with the regulations; and (3) failure to prepare and maintain adequate and accurate case histories.

- On November 17, 2004, CBER issued a Warning Letter to Daniel Amsterdam, Ph.D., Erie County Medical Center Corp., Buffalo, New York. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; and (2) failure to prepare and maintain adequate and accurate case histories.

- On November 17, 2004, and on May 26, 2005, CBER issued Warning Letters to Niel Constantine, Ph.D., University of Maryland School of Medicine, Baltimore, Maryland. (Note: Separate Warning Letters citing different violations.)
- The Warning Letters included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to obtain

informed consent in accordance with the regulations; (3) failure to prepare and maintain adequate and accurate case histories; (4) failure to maintain adequate, complete, and current records relating to the receipt, use, and disposition of the products; (5) failure to submit required reports to the Institutional Review Board; and (6) failure to submit a complete and accurate final report to the sponsor.

- On May 13, 2005, CBER issued a Warning Letter to Janet Lowther, Gulf Coast Regional Blood Center, Houston, Texas; and May 16, 2005, CBER issued a Warning Letter to Daniel Cohen, M.D., Fenway Community Health, Boston, Massachusetts. The Warning Letters included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to prepare and maintain adequate and accurate case histories; and (3) failure to maintain adequate, complete, and current records relating to the receipt, use, and disposition of the products.

- On May 16, 2005, CBER issued a Warning Letter Thomas Koppes, Berwyn, Illinois. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to prepare and maintain adequate and accurate case histories; (3) failure to maintain adequate, complete, and current records relating to the receipt, use, and disposition of the products; and (4) failure to ensure that the investigation was conducted according to the conditions of approval imposed by the institutional review board.

- On June 10, 2005, Alison Jones, Tapestry Health Systems, Inc., Florence, Massachusetts. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to obtain informed consent in accordance with the regulations; (3) failure to prepare and maintain adequate and accurate case histories; and (4) failure to maintain adequate, complete, and current records relating to the receipt, use, and disposition of the products.

- On August 23, 2005, Michael Gottlieb, M.D., Synergy Hematology-Oncology Associates, Los Angeles, California. The Warning Letter identified the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure

to ensure that the investigation was conducted according to the investigational plan; (2) failure to prepare and maintain adequate and accurate case histories; and (3) failure to maintain adequate, complete, and current records relating to the receipt, use, and disposition of the products.

Warning Letters Issued to Two Clinical Investigators Conducting Studies with Investigational Biological Drugs

CBER issued Warning Letters to the following clinical investigators conducting research using investigational biological products in human subjects:

- On October 4, 2004, CBER issued a Warning Letter to Jon Richards, M.D., Ph.D., Park Ridge, Illinois. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; and (2) failure to assure Institutional Review Board review by not promptly reporting changes in the research activity.

- On June 6, 2005, CBER issued a Warning Letter to Robert Hostoffer, D.O., South Euclid, Ohio. The Warning Letter included the following violations: (1) failure to protect the rights, safety, and welfare of subjects under the investigator's care, and failure to ensure that the investigation was conducted according to the investigational plan; (2) failure to obtain informed consent in accordance with the regulations; and (3) failed to maintain adequate records of the disposition of the investigational drug.

Each Warning Letter advised the clinical investigator that the failure to effectively implement corrective actions and/or the commission of other violations may warrant the initiation of enforcement actions without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs or devices, and/or injunction. Each clinical investigator provided corrective actions plans to prevent the recurrence of the violations.

Warning Letters Issued to Efoora Inc., and Saliva Diagnostic Systems, Inc.

On August 25, 2005, CBER issued Warning Letters to Efoora, Inc., Buffalo Grove, Illinois, and Saliva Diagnostics Systems, Inc., Framingham, Massachusetts. Each firm is developing a rapid HIV test kit. The Warning Letters included the following violations: (1) failure to ensure proper monitoring of the investigation; (2) failure to

use monitors qualified by training and experience; (3) failure to submit a complete Investigational Device Exemption application to FDA, (4) failure to ensure that FDA was promptly informed of significant information about an investigation, and initiated part of an investigation before FDA approved the supplemental application; and (5) failure to prepare and submit a current investigator list.
Each Warning Letter advised the sponsor that the failure to effectively implement corrective actions and/or the commission of other violations may warrant the initiation of enforcement actions without further notice.

Clinical Investigator Roy C. Page, M.D., Sentenced

Clinical Investigator, Roy C. Page, M.D., of Memphis, Tennessee, was sentenced in federal court on August 3, 2005, for introduction and delivery for introduction of a misbranded drug into interstate commerce. Page was sentenced to one year probation and a $2,000 fine.

In 2003, Page signed a Consent Agreement with CBER in which he agreed to be permanently disqualified as a clinical investigator. Page is no longer eligible to receive investigational new drugs, animal drugs, biologics, devices, or food additives, and shall not be entitled to conduct any further studies of investigational products regulated by FDA.

Page was involved in the study of investigational drugs for use in the treatment of cancer.

Blood and Biologic Products

Actions Taken Under the Consent Decree for the American Red Cross

American Red Cross Received Adverse Determination Letter for Numerous Deviations from FDA Laws, Regulations and Consent Decree

On March 28, 2005, an Adverse Determination Letter (ADL) was issued to the American Red Cross (ARC) under paragraph VIII of the Amended Consent Decree of Permanent Injunction (Decree) entered on April 15, 2003, that included the assessment of a penalty of $540,000. The letter addressed observations cited on FDA 483s issued after inspections of the ARC's Irvine, California, location, conducted July 19 - August 4, 2004 and November 29 - December 13, 2004.

During these inspections, FDA investigators observed numerous deviations from the FDA law, regulations, and the Decree. The deviations included the failure to follow written production and process control procedures which require physical and electronic control of suspect blood products, failure to conduct a thorough investigation of unexplained discrepancies or failures, and failure to maintain written procedures that include all steps to be followed in the manufacture of blood and blood components. As a result of the deviations, 10 units of suspect whole blood were released from quarantine, were manufactured into 20 blood components, and were distributed in commerce.

On May 16, 2005, an ADL was issued to ARC under paragraph X. of the Decree that included the assessment of a penalty of $3,405,000 for the distribution of 1,442 unsuitable blood components. A penalty of up to $3,000 per component was assessed for the release of 1,441 unsuitable blood components and $10,000 for the re-release of one unsuitable blood component, based on FDA's evaluation of the circumstances related to each release and the factors prescribed by the Decree under paragraphs X.A.2. and X.C.

Warner-Lambert Consent Decree Vacated for Rochester Facility

On August 16, 1993, the United States District Court for the District of New Jersey entered a Consent Decree of Permanent Injunction against the Warner-Lambert Company and two individuals. The Decree was based on non-compliance with current good manufacturing practice for both drug and biological products.

In February of 1998, Warner-Lambert sold its Rochester, Michigan, facility to Parkedale Pharmaceuticals, Inc. (Parkedale), a wholly owned subsidiary of King Pharmaceuticals, Inc. (King). King agreed to assume the responsibilities of Warner-Lambert under the Consent Decree respecting the Rochester facility.

In a letter dated March 11, 2005, King, through its counsel, noted its intentions to pursue the possibility of vacating the Consent Decree of Permanent Injunction applicable to the King facility located in Rochester, Michigan. Upon concluding that all of the requirements listed in the Consent Decree had been satisfied, FDA joined with the firm's motion to vacate the injunction, and the Warner-Lambert Consent Decree of Permanent Injunction with regard to the Rochester, Michigan facility was vacated on July 18, 2005.

Internet Enforcement

Warning Letters Issued to Internet Sites for Unlicensed Biological Products

ZooScape.com

Warning Letter Issued for Product Promoted on Internet as Homeopathic Smallpox Vaccine

On April 22, 2005, CBER issued a Warning Letter to ZooScape.com. The Warning Letter was issued following a review by FDA of the firm's Internet website. The review determined that the firm's product "Vaccininum-Injeel" was being promoted for conditions that caused it to be a drug and further, that it was promoted as a homeopathic Smallpox vaccine.

The Warning Letter also noted that the order page of the website provided for payment and shipment of the firm's product to U.S. addresses. Furthermore, the order page displayed the price for the product in U.S. currency.

FDA also raised concerns in the Warning Letter about the false and misleading information on the website regarding effectiveness claims and the lack of adequate descriptions of the risks, warnings and contraindications of the product, and failure to require a prescription for the product.

Heel Inc. (Heelusa.com)

On January 3, 2005, CBER issued a Warning Letter to Heel, Inc. The Warning Letter was issued following a review by FDA of the firm's Internet website. The review determined that the firm's products "Engysto and Gripp-Heel" were being promoted for conditions that caused them to be drugs and further, that they were promoted as homeopathic influenza vaccines.

The Warning Letter also noted that the products appeared to be for sale to U.S. citizens and the order page of the website provides for payment and shipment to U.S. addresses. The products appeared to be available to anyone who ordered the products from the website.

FDA also raised concerns in the Warning Letter about the false and misleading information on the website regarding effectiveness claims and the lack of adequate descriptions of the risks, warnings and contraindications of the product, and failure to require a prescription for the product.

Immunity Today, LLC (immunitytoday.com)

On June 2, 2005, CBER issued a Warning Letter to Immunity Today LLC. The Warning Letter was issued following a review by FDA of the firm's Internet website. The review determined that the firm's "transfer factor" products, derived from bovine colostrum, were being promoted for conditions that caused them to be drugs and further, that were purported to prevent and treat a variety of conditions including cancer and HIV.

The Warning Letter also noted that the order page of the website provided for payment and shipment of the firm's product to U.S. addresses. Furthermore, the order page displayed the price for the product in U.S. currency.

The Warning Letter advised that in order to introduce or deliver for introduction a biologic into interstate commerce, a valid biologics license must be in effect. The Warning Letter stated, "Your products are not the subject of an approved biologics license application (BLA) or an investigational new drug application (IND). Therefore, your shipments of product represent violations of the Act and/or the PHS Act."

Vaccines

Warning Letter Issued to Chiron Corporation

FDA and UK's Medicines and Healthcare Products Regulatory Agency Worked Together to Address Manufacturing Deficiencies at Chiron Corporation

On October 5, 2004, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) suspended Chiron Corporation's license to manufacture influenza vaccine due to good manufacturing practice deficiencies that led to sterility failures in filled vials of the vaccine. Chiron Corporation is an influenza virus vaccine manufacturer located in Liverpool, United Kingdom. FDA and MHRA's review of Chiron's investigation of the root cause of the company's sterility failures and FDA's own review and inspections of Chiron's facility pointed to problems that led FDA to conclude that the sterility, and therefore safety, of the vaccine Chiron produced for the 2004-2005 influenza season could not be assured.

On December 9, 2004, FDA issued a Warning Letter to Chiron Corporation, based on significant objectionable conditions observed during FDA's inspection conducted October 10-15, 2004. The letter identified deviations from current good manufacturing practice in the manufacture of Influenza Virus Vaccine, Fluvirun®,

which included, failure to establish an adequate quality control unit, failure of the quality control unit to review production records to assure no errors have occurred, or, if errors have occurred, that they are fully investigated, and failure to establish an adequate system for monitoring environmental conditions of aseptic processing areas.

After MHRA's suspension of Chiron's license to manufacture influenza virus vaccine at the Liverpool facility, Chiron gave MHRA and FDA permission to discuss information that could not otherwise be shared. This arrangement allowed free exchange of information as the company initiated efforts to address the problems at Liverpool. Chiron developed an extremely comprehensive remediation plan. FDA and MHRA reviewed and provided extensive input on this plan and continued to provide extensive feedback to Chiron as it implemented the remediation plan. As a result of progress in the Liverpool facility, MHRA lifted its license suspension on March 2, 2005, which allowed Chiron to proceed with manufacturing plans.

FDA and MHRA also worked together and actively communicated on inspectional activities. FDA accompanied MHRA on work-in-progress inspections of the Chiron Liverpool facility in December 2004, February, May and September 2005, and MHRA accompanied FDA on its comprehensive inspection of the Liverpool facility in July 2005. In August 2005, FDA communicated to Chiron that its responses to the FDA inspectional observations were generally acceptable.

The full text of FDA's Warning Letter to Chiron Corporation is available on FDA's web site at: http://www.fda.gov/foi/warning_letters/g5103d.htm.

Violative Advertising and Promotion

Warning Letters Issued for Violative Advertising and Promotion

Ovation Pharmaceuticals, Inc.

Sales Brochure Failed to Reveal Material Facts Regarding Risks Associated with Use of Product

On June 2, 2005, CBER issued a Warning Letter to Ovation Pharmaceuticals, Inc., Deerfield, Illinois, for failure to reveal material facts regarding the risks associated with the use of Panhematin (hemin for injection). Specifically, a sales brochure failed to provide risk information (contraindications, warnings, precautions, and adverse reaction information) and a product monograph did not include complete risk information. In addition, both the brochure and monograph implied that

Panhematin was indicated for treatment of all porphyries, an indication broader than approved.

The Warning Letter stated, "Your brochure and monograph misbrand PANHEMATIN within the meaning of section 502(a) of the Act because they fail to reveal material facts regarding the risks associated with the use of this product and do not make clear that the product is not indicated for porphyria cutanea tarda. In addition, the brochure misbrands PANHEMATIN within the meaning of section 502(f) of the Act if it is disseminated without the FDA-approved professional labeling (PI). (21 U.S.C. 352(a), 352(f); see 321(n))."

FDA requested that Ovation Pharmaceuticals immediately cease the dissemination of promotional materials for Panhematin containing the same or similar issues to the ones cited in the letter. Because of the serious nature of the violation, Ovation Pharmaceuticals was also asked to submit a plan of action to FDA to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials.

OCTAPHARMA Phatmazeutika Produktionsges, m.b.H.

Firm's File Card and Website Contain Unsubstantiated Safety, Effectiveness, and/or Superiority Claims in Violation of the FD&C Act

On August 31, 2005, CBER issued a Warning Letter to the U.S. Agent for OCTAPHARMA, Centerville, Virginia, because the firm disseminated a file card, dosage guide and website that were misleading because the information failed to reveal material facts regarding the risks associated with Octagam 5% [Immune Globulin Intravenous (Human)] and, therefore, misbranded Octagam in violation of the Federal Food, Drug, and Cosmetic Act (the Act). In addition, the file card and website contained unsubstantiated safety, effectiveness, and/or superiority claims in violation of the Act. Lastly, Octapharma failed to submit promotional materials to CBER at the time of initial dissemination of those materials.

Specifically, the FDA-approved professional labeling/package insert (PI) for Octagam includes a black box warning regarding reports of renal dysfunction, acute renal failure, osmotic nephrosis, and death associated with the use of Immune Globulin Intravenous (Human) (IGIV) products and includes a warning regarding products made from human plasma. However, Octapharma provided no information on what specific adverse events were associated with this product and did not provide complete information regarding contraindications, black box warnings, and other warnings. The file card was disseminated without a PI. The failure to disseminate the file card with the PI misbranded the product. Octapharma also failed to submit promotional materials to CBER at the time of dissemination of these materials, in violation of the regulations.

In addition, Octapharma also made the following misleading claims that misbranded Octagam: "Unsurpassed viral safety," and, "Over the past ten years, data from more than 6,100 patients and 90,000 treatment episodes has been gathered." Immediately following the paragraph containing this statement, it stated, "No viral transmissions have ever been observed. This proves the excellent safety record of Octagam." These safety claims were unsupported by substantial evidence. These data represented a post-marketing study in Europe where questionnaires were sent out and responses were voluntary.

Such data did not constitute substantial evidence in support of claims because the monitoring of safety and effectiveness outcomes was not uniform across centers or within centers, the data were subject to observation and reporting bias, and they could not be verified by independent study monitors. In addition, such statements implicitly overstated the clinical experience which supported Octagam approval in the U.S. and resulted in a misleading message.